AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions of the claims and listing of the claims in the application.

Listing of claims:

1. (Currently Amended) A pseudo-sequence method for ~~comparing~~ identifying similarities in binding sites of a first 7TM receptor with those of one or more further 7TM receptors, ~~with respect to~~ by comparing the physicochemical properties of selected amino acid residues of their binding sites, the method comprising the steps of:

~~i) optionally, aligning part of or all of the amino acid sequence of the first 7TM receptor with part of or all of the amino acid sequence of the one or more further 7TM receptors,~~

~~ii) selecting, in a sequential or non-sequential order, at the most 12 amino acid residues per helix and/or extracellular loops, which are involved in one or more binding sites of each 7TM receptor,~~

~~iii) forming a pseudo-sequence comprising at the most 50 amino acid residues from the selected sequential or non-sequential amino acid residues,~~

[[iv)]]i) ~~for each 7TM receptor~~ using a pseudo-sequence for the first and each of the one or more further 7TM receptor, in which the pseudo-sequence comprises amino acid residues involved in the binding sites or potential binding sites of the first and the one or more further 7TM receptors, to assign~~ing~~ one or more physicochemical descriptors to the amino acid residues of the ~~selected amino acid~~ pseudo-sequence, ~~involved in one or more binding sites~~ wherein the one or more physicochemical descriptors reflect 7TM receptor-ligand interaction features,

[[v)]]ii) optionally, for each 7TM receptor mathematically manipulating the physicochemical descriptors of step [[iv)]]i) to obtain a simplified measure of the physicochemical properties of the binding site,

[[vi)]]iii) for each of the one or more further 7TM receptor, generating a similarity score ~~as defined herein~~ by comparing the physicochemical descriptor or~~, if relevant,~~ the simplified measure thereof for the first 7TM receptor with the physicochemical descriptors

or~~, if relevant,~~ the simplified measures thereof for each of the one or more further 7TM receptors, in which the similarity score quantifies how similar the identified binding sites or potential binding sites of the first 7TM receptor are to those of each of the one or more further 7TM receptors, and

[[vii)]]iv) optionally, ranking the one or more further 7TM receptors with respect to the physicochemical properties of their binding sites according to their similarity scores obtained in step [[vi)]]iii), to identify which of the one or more further 7TM receptors have similar binding properties to those of the first 7TM receptor.

2. (Original) A method according to claim 1, wherein the comparison is made without using data related to binding affinity of a ligand to a 7TM receptor.

3. (Currently Amended) A method according to claim 1 [[for]], further comprising classifying 7TM receptors according to the physicochemical properties of their binding sites.

4. (Original) A method according to claim 3, wherein the classification is made without using data related to binding affinity of a ligand to a 7TM receptor.

5. (Currently Amended) A method according to claim [[1]] 44, wherein step [[ii)]] vi) as defined in claim [[1]] 44 comprises selecting, in a sequential or non-sequential order, at the most 11 amino acid residues per helix and/or extracellular loops, which are involved in one or more binding sites of each 7TM receptor.

6. (Currently Amended) A method according to claim [[1]] 44, wherein step [[iii)]] vii) as defined in claim [[1]] 44 comprises forming a pseudo-sequence comprising at the most 50 amino acid residues from the selected sequential or non-sequential amino acid residues.

7. (Withdrawn and Currently Amended) A drug discovery method for identifying ligands, which bind to a first 7TM receptor and potentially bind to one or more further 7TM receptors, the method comprising the steps of i) to [[vii)]] iv) as defined in claim 1 and the further steps of

viii) selecting from one to about 100 further 7TM receptors which have the closest similarity scores to the first 7TM receptor,

ix) identifying ligands which potentially bind to those further OTIS receptors selected in step vii) by selecting ligands that bind to the first 7TM receptor.

8. (Withdrawn and Currently Amended) A drug discovery method for identifying ligands which bind to a first 7TM receptor and to one or more further 7TM receptors, the method comprising the steps of i) to [[vii)]] iv) as defined in claim 1 and the further steps of:

viii) selecting from one to about 100 further 7TM receptors which have the closest similarity scores to the first 7TM receptor,

ix) screening ligands that bind to the first 7TM receptor against the selected 7TM receptors of step viii).

9. (Withdrawn and Currently Amended) A drug discovery method for identifying a potential lead compound for a first 7TM receptor, the method comprising the steps of i) to [[vii)]] iv) as defined in claim 1 and the further steps of

viii) selecting from one to about 100 further 7TM receptors which have the closest similarity scores to the first 7TM receptor,

ix) identifying ligands that bind to said one or more further 7TM receptors to construct a library including a potential lead compound for the first 7TM receptor.

10. (Withdrawn and Currently Amended) A drug discovery method for identifying a lead compound for a first 7TM receptor, the method comprising the steps of i) to [[vii)]] iv) as defined in claim 1 and the further steps of

viii) selecting from one to about 100 further 7TM receptors which have the closest similarity scores to the first 7TM receptor,

ix) identifying ligands that bind to said one or more further 7TM receptors to construct a library, and

x) screening said library against the first 7TM receptor to identify a lead compound for the first 7TM receptor.

11. (Withdrawn and Currently Amended) A drug discovery method for constructing a pharmacophore model for a first 7TM receptor, the method comprising the steps of i) to [[vii)]] iv) as defined in claim 1 and the further steps of

viii) selecting from one to about 100 further 7TM receptors which have the closest similarity scores to the first 7TM receptor,

ix) identifying ligands that bind to said one or more further 7TM receptors to construct a pharmacophore model.

12. (Withdrawn) A drug discovery method according to claim 10, wherein the first 7TM receptor is one for which no ligands have been identified.

13. (Withdrawn) A drug discovery method according to claim 10, wherein the first 7TM receptor is an orphan receptor.

14. (Withdrawn and Currently Amended) A method according to claim [[1]] 7, wherein from one to 50 further 7TM receptors is/are selected in step viii).

15. (Withdrawn and Currently Amended) A method according to claim [[1]] 7, wherein from one to 25 further 7TM receptors is/are selected in step viii).

16. (Withdrawn and Currently Amended) A method according to claim [[1]] 7, wherein from one to 15 further 7TM receptors is/are selected in step viii).

17. (Previously Presented) A method according to claim 1, wherein the method is executed by a computer under the control of a program and the computer includes a memory for storing said program.

18. (Currently Amended) A method according to claim [[1]] 44, wherein ~~step i) is included and~~ the alignment in step v) is based on a model developed for 7TM receptors.

19. (Previously Presented) A method according to claim 18, wherein the 7TM receptors are Class A, Class B, Class C or taste receptors.

20. (Currently Amended) A method according to claim [[1]] 44, wherein ~~step i) is included and~~ the alignment in step v) is made with respect to transmembrane positioning of α-helices of 7TM receptors.

21. (Previously Presented) A method according to claim 1, wherein the binding site includes amino acid residues located in one or more extracellular loops of the 7TM receptors.

22. (Previously Presented) A method according to claim 1, wherein the binding site includes amino acid residues located in one or more subsites of the binding site and in one or more extracellular loops of the 7TM receptors.

23. (Previously Presented) A method according to claim 1, wherein the physicochemical descriptors reflect 7TM receptor-ligand interaction features of the amino acid residues.

24. (Previously Presented) A method according to claim 1, wherein the physicochemical descriptors are chosen to reflect hydrophobic, electronic, steric, hydrogen bonding or other properties of the amino acid residues.

25. (Previously Presented) A method according to claim 1, wherein the physicochemical descriptors reflect 3-dimensional features of the amino acid residues.

26. (Previously Presented) A method according to claim 1, wherein the physicochemical descriptors are selected from descriptors used in quantitative structure-activity relationships (QSAR), Principle Component Regression (PCR) and Partial Least-Squares (PLS) analysis of peptides.

27. (Previously Presented) A method according to claim 23, wherein the physicochemical descriptors are selected from molecular weight (MW), van der Waals volume, van der Waals radius, molar refractivity (MR), STERIMOL parameters (L, B_1, B_5), Parachor (P_r), polar surface area, non-polar

surface area, total surface area, ionisation constant (pK_{COOH}, PK_{NH2}), isoelectric point, net charge at pH 7, partition coefficient (log P), calculated partition coefficient (clog P, Prolog P, Maclog P), distribution coefficient (log D), TLC retention time, HPLC retention time, HPLC capacity factor log k, ^{1}H NMR chemical shift, ^{13}C NMR chemical shift, steric and electrostatic 3D-property MS-WHIM indexes, calculated interaction energies, isotropic surface area (ISA), electronic charge index (ECI), charge transfer for carbons (CT), Lewis basicity (LB), Lewis acidity (LA), maximum electrostatic potential (V_{max}), minimum electrostatic potential (V_{min}), maximum local ionization energy (I_{max}), minimum local ionization energy (I_{min}), conformational strain energy (ΔH_{strain}), molecular electrostatic potential (MEP) on Connolly molecular surface, local flexibility (Fr), flexibility index (Fb), chain flexibility (FO), occupied volume by a residue buried in globular protein, bulkiness defined as the ratio of the side-chain volume to its length, total energy (E_{total}), heat of formation (ΔH_f), energy of highest occupied molecular orbital (E_{HOMO}), energy of lowest unoccupied molecular orbital (E_{LUMO}), dipole moment (μ), polarizability (a), most positive partial charge on a hydrogen atom (qH+), most negative partial charge in the molecule (q-), partial charges on the oxygen and carbon atoms (qC, qO) of the carbonyl group, integrated molecular transform (FTm), integrated electronic transform (FTe), Integrated charge transform (FTc), normalized molecular moment (Mn), electronic moment (Me), charge moment (Mc), absolute electronegativity (EN), absolute hardness (HA).

28. (Previously Presented) A method according to claim 17, wherein the physicochemical descriptors include indicator variables.

29. (Original) A method according to claim 28, wherein the indicator variables denote absence or presence of aromatic side chains, hydrophobic side chains, negatively charged side chains, positively charged side chains, polar side chains, hydrogen-bond donating side chains, hydrogen-bond accepting side chains and/or other selected features.

30. (Currently Amended) A method according to claim 1 ~~including step v)~~, wherein the physicochemical descriptors are weighted in step [[v)]] ii).

31. (Currently Amended) A method according to claim 1 ~~including step v)~~, wherein a simplified measure of the physicochemical properties of the binding site is obtained from principal component analysis (PCA) of the physicochemical descriptors.

32. (Withdrawn and Currently Amended) A method according to claim 1, wherein the generation of a similarity score in step [[vi)]] iii) is based upon a pattern recognition method.

33. (Withdrawn) A method according to claim 1, wherein the generation of the similarity score involves a Principal Component Analysis (PCA) reducing the number of descriptors to a few principal components.

34. (Withdrawn and Currently Amended) A method according to claim 1, wherein the generation of the similarity score in step [[vi)]] iii) is based upon Euclidian Distance Measure: $d(F1,F2) = \text{sqrt}\ (F1 - F2)^2$.

35. (Currently Amended) A method according to claim 28, wherein the generation of the similarity score in step [[v)]] iii) is based upon a Tanimoto Similarity Measure: TC = BC / (B1 + B2 - BC).

36. (Withdrawn and Currently Amended) A method according to claim 28, wherein the generation of the similarity score in step [[vi)]] iii) is based upon a Tversky Similarity Measure: TC = BC / (α * B1 Unique + β* B2Unique + BC), wherein α are prototype features and β variant features.

37. (Currently Amended) A method according to claim 1, wherein the step [[vii)]] iv) is included.

38. (Withdrawn) A method according to claim 1, wherein the similarity score or, if relevant, the ranking is based upon a 2- or 3-dimensional graphical representation.

39. (Withdrawn) Use of a pharmacophore according to claim 11 for *in silico* screening.

40. (Withdrawn) Use of a pharmacophore according to claim 11 for construction of a library.

41. (Withdrawn) Use of a pharmacophore according to claim 11 for design of a ligand.

42. (Withdrawn) Use of a method according to claim 1 to identify receptors, which are likely to cause a selectivity problem during drug development of a drug interacting with a given receptor.

43. (Withdrawn) Use of a method according to claim 1 to identify differences in subsites of binding sites between 7TM receptors as means to improve receptor selectivity of a drug towards a given 7TM receptor.

44. (New) A method according to claim 1, comprising the further steps of:

v) if not already aligned, aligning part of or all of the amino acid sequence of the first 7TM receptor with part of or all of the amino acid sequence of the one or more further 7TM receptors and using the aligned sequences to identify one or more binding sites or potential binding sites of the first and one or more further 7TM receptors,

vi) selecting, in a sequential or non-sequential order, at the most 12 amino acid residues per helix and/or extracellular loops, which are involved in the identified one or more binding sites of each 7TM receptor, and

vii) forming a pseudo-sequence for each 7TM receptor comprising at the most 50 amino acid residues from the selected sequential or non-sequential amino acid residues, for use in step i).

45. (New) A computer readable medium carrying a computer program arranged to identify similarities in binding sites of a first 7TM receptor with those of one or more further 7TM receptors, by comparing the physicochemical properties of selected amino acid residues of their binding sites, by executing the steps of:

i) using a pseudo-sequence for the first and each one or more further 7TM receptor, which pseudo-sequences comprise amino acid residues involved in the binding sites or potential binding sites of the first and one or more further 7TM receptors, to assign one or more physicochemical descriptors to the amino acid residues of the amino acid pseudo-sequence, which physicochemical descriptors reflect 7TM receptor-ligand interaction features,

ii) optionally, for each 7TM receptor mathematically manipulating the physicochemical descriptors of step i) to obtain a simplified measure of the physicochemical properties of the binding site,

iii) for each one or more further 7TM receptor, generating a similarity score by comparing the physicochemical descriptor or the simplified measure thereof for the first 7TM receptor with the physicochemical descriptors or the simplified measures thereof for the one or more further 7TM receptors, which scores quantify how similar the identified binding sites or potential binding sites of the first 7TM receptor are to those of the one or more further 7TM receptors, and

iv) optionally, ranking the 7TM receptors with respect to the physicochemical properties of their binding sites according to the similarity scores obtained in step iii),to identify which of the one or more further 7TM receptors have similar binding properties to those of the first 7TM receptor.